Amendments to the claims:

Please cancel claim 87.

This listing of claims will replace all prior versions, and listings, of claims in the application:

1-78. (canceled)

79. (currently amended) A method of creating, in an isolated mouse embryonic stem (ES) cell, a modified endogenous gene locus flanked downstream by a site-specific recombination site comprising:

(a) providing a large targeting vector produced by bacterial homologous recombination for use in eukaryotic cells (LTVEC) comprising a site-specific recombination site, a downstream homology arm containing a region homologous to a 3' end of the endogenous gene locus region and an upstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511 and lox2272;

(b) introducing the LTVEC of (a) into an isolated mouse ES cell; and

(c) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous gene locus of the cell, wherein the endogenous gene locus is flanked downstream by the site-specific recombination site.

80. (currently amended) A method of creating, in an isolated mouse embryonic stem (ES) cell, a modified endogenous gene locus flanked upstream by a site-specific recombination site comprising:

(a) creating a large targeting vector by bacterial homologous recombination for use in eukaryotic cells (LTVEC) comprising a site-specific recombination site, an upstream homology arm containing a region homologous to the 5' end of the endogenous gene locus region and a downstream homology arm within the locus, wherein the homology arms are larger than 20 kb and a site-specific recombination site is selected from one or more of loxP, lox511 and lox2272;

(b) introducing the LTVEC of (a) into an isolated mouse ES cell; and

(c) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous gene

locus of the cell, wherein the endogenous gene locus is flanked upstream by the site-specific recombination site.

81. (currently amended) A method of creating, in an isolated mouse embryonic stem (ES) cell, a modified endogenous gene locus flanked by site-specific recombination sites comprising:

(a) creating a first large targeting vector by bacterial homologous recombination for use in eukaryotic cells (LTVEC) comprising the site-specific recombination site, a downstream homology arm containing a region homologous to the 3' end of the endogenous gene locus region and an upstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511 and lox2272;

(b) creating a second LTVEC by bacterial homologous recombination comprising the site-specific recombination site, an upstream homology arm containing a region that flanks the 5' end of the endogenous gene locus region and a downstream homology arm within the locus;

(c) introducing the first and second LTVECs into an isolated mouse ES cell; and

(d) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous gene locus of the cell, wherein the site-specific recombination sites are flanking the endogenous gene locus.

82. (previously presented) The method of claim 81, further comprising:

(e) introducing a recombinase into the cell identified in step (d), wherein the endogenous gene locus flanked by the site-specific recombination sites is deleted.

83. (previously presented) The method of claim 82, further comprising:

(f) creating a vector containing the site-specific recombination sites flanking a replacing gene locus; and

(g) introducing the vector of (f) into the cell of (e) such that, through recombination, the replacing gene locus is inserted between the site-specific recombination sites.

84. (previously presented) The method of claim 82, further comprising:

(f) obtaining a large cloned genomic fragment containing, in whole or in part, a replacing region gene locus;

(g) using bacterial homologous recombination to genetically modify the cloned fragment of (f) to create a third LTVEC comprising the replacing region gene locus flanked by a downstream homology arm containing a region homologous to the 3' end of the endogenous gene locus region and an upstream homology arm containing a region homologous to the 5' end of the endogenous gene locus region; and

(h) introducing the third LTVEC of (g) into the cell of (e) to replace the deleted endogenous gene locus.

85. (previously presented) The method of claim 82, wherein the recombinase is CRE.

86. (previously presented) The method of claim 79, 80 or 81, wherein the quantitative assay comprises quantitative PCR, FISH, comparative genomic hybridization, isothermic DNA amplification, or quantitative hybridization to an immobilized probe.

87. (canceled)

88. (currently amended) A method of creating, in an isolated mouse embryonic stem (ES) cell, a modified endogenous immunoglobulin variable region gene locus flanked downstream by a site-specific recombination site comprising:

(a) creating a large targeting vector by bacterial homologous recombination for use in eukaryotic cells (LTVEC) comprising a site-specific recombination site, a downstream homology arm containing a region homologous to a 3' end of the endogenous immunoglobulin variable region gene locus region and an upstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511 and lox2272;

(b) introducing the LTVEC of (a) into an isolated mouse ES cell; and

(c) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous immunoglobulin variable region gene locus of the cell, wherein the endogenous immunoglobulin variable region gene locus is flanked downstream by the site-specific recombination site.

89. (currently amended) A method of creating, in an isolated mouse embryonic stem (ES) cell, a modified endogenous immunoglobulin variable region gene locus flanked upstream by a site-specific recombination site comprising:

(a) creating a large targeting vector by bacterial homologous recombination for use in eukaryotic cells (LTVEC) comprising a site-specific recombination site, an upstream homology arm containing a region homologous to the 5' end of the endogenous immunoglobulin variable region gene locus region and a downstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511 and lox2272;

(b) introducing the LTVEC of (a) into an isolated mouse ES cell; and

(c) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous immunoglobulin variable region gene locus of the cell, wherein the endogenous immunoglobulin variable region gene locus is flanked upstream by the site-specific recombination site.

90. (currently amended) A method of creating, in an isolated mouse embryonic stem (ES) cell, a modified endogenous immunoglobulin variable region gene locus flanked by site-specific recombination sites comprising:

(a) creating a first large targeting vector by bacterial homologous recombination for use in eukaryotic cells (LTVEC) comprising the site-specific recombination site, a downstream homology arm containing a region homologous to the 3' end of the endogenous immunoglobulin variable region gene locus region and an upstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511 and lox2272;

(b) creating a second LTVEC by bacterial homologous recombination comprising the site-specific recombination site, an upstream homology arm containing a region that flanks the 5' end of the endogenous immunoglobulin variable region gene locus region and a downstream homology arm within the locus;

(c) introducing the first and second LTVECs into an isolated mouse ES cell; and

(d) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference

gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous immunoglobulin variable region gene locus of the cell, wherein the site-specific recombination sites are flanking the endogenous immunoglobulin variable region gene locus.

91. (previously presented) The method of claim 90, further comprising:

(e) introducing a recombinase into the cell identified in step (d), wherein the endogenous immunoglobulin variable region gene locus flanked by the site-specific recombination sites is deleted.

92. (previously presented) The method of claim 91, further comprising:

(f) creating a vector containing the site-specific recombination sites flanking a human immunoglobulin variable region gene locus; and

(g) introducing the vector of (f) into the cell of (e) such that, through recombination, the human immunoglobulin variable region gene locus, in whole or in part, is inserted between the site-specific recombination sites.

93. (previously presented) The method of claim 90, further comprising:

(f) obtaining a large cloned genomic fragment containing, in whole or in part, a human immunoglobulin variable region gene locus;

(g) using bacterial homologous recombination to genetically modify the cloned fragment of (f) to create a third LTVEC comprising the replacing region gene locus flanked by a downstream homology arm containing a region homologous to the 3' end of the endogenous gene locus region and an upstream homology arm containing a region homologous to the 5' end of the endogenous gene locus region; and

(h) introducing the third LTVEC of (g) into the cell of (e) to replace the deleted endogenous gene locus.

94. (currently amended) A method of replacing, in an isolated mouse embryonic stem (ES) cell, in whole or in part, an endogenous immunoglobulin variable region gene locus with part or all of a human immunoglobulin variable region gene locus comprising:

(a) creating a first large targeting vector by bacterial homologous recombination for use in eukaryotic cells (LTVEC) comprising a site-specific recombination site, a downstream homology

arm containing the region immediately adjacent to, but not including, the J segments of the immunoglobulin variable gene locus region and an upstream homology arm within the variable gene locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511 and lox2272;

(b) creating a second LTVEC comprising a site-specific recombination site, an upstream homology arm containing the region adjacent to the most distal V gene segment, but not containing any V gene segments of the immunoglobulin variable gene locus region and a downstream homology arm within the variable gene locus, wherein the homology arms are larger than 20 kb;

(c) introducing the first and second LTVECs into an isolated cell;

(d) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the variable gene locus of the cell, wherein the site-specific recombination sites flank the endogenous variable region gene locus;

(e) creating a vector containing the site-specific recombination sequences flanking all or part of a human immunoglobulin variable gene locus; and

(f) introducing the vector of (e) into the identified cell such that, through recombination, the endogenous immunoglobulin variable region gene locus is replaced, in whole or in part, with all or part of a human immunoglobulin variable gene locus gene locus.